## REMARKS/ARGUMENTS

***Status of the Claims***

Upon entry of the present amendment, claims 4-8 and 15-18 are pending. Claims 19-23 are canceled without disclaimer or prejudice to renewal. Claims 4-6 and 18 are amended. Claims 4-6 are amended to set forth that the growth medium is supplemented with a combination of growth factors consisting of hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2). Support is found, for example, on page 13, lines 23-25; on page 15, lines 10-11; and on page 29, line 23 through page 30, line 1. Support for amending claim 18 is found, for example, on page 37, line 16 through page 38, line 6 and in Figures 5a-5c.

No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

***Telephonic Interview***

The Examiner is thanked for graciously granting the telephonic interview of September 5, 2008. The issues discussed are as set forth in the present Office Action and herein.

***Rejection under 35 U.S.C. § 112, first paragraph, new matter***

The Examiner has rejected claims 6 and 18-21 under 35 U.S.C. § 112, first paragraph, as allegedly introducing new matter.

With respect to claims 6 and 18, Applicants do not agree with the Examiner's position. However, in the interest of furthering prosecution, Applicants have amended claim 18, to set forth that the population of cells differentiated from the neural stem cell comprises more neurons than glia cells. Applicants acknowledge that the text at page 37, lines 16-18 states that when HGF was added to the medium during differentiation, neurons were obtained more than astrocytes. However, Applicants respectfully point out to the Examiner that the text on page 37, lines 19 and 23 teaches that when HGF was added to the differentiation medium, more than 50% of the cells were neurons. Figures 5a, 5b and 5c depict these findings in graphic format: when HGF is added to the differentiation medium, more than 50% of the cells are neurons; less than

50% of the cells are comprised of astrocytes, oligodendrocytes, *and other cell types combined.* Applicants also respectfully point out that the percentage of other cell types (about 10%) is greater than the percentage of oligodendrocytes in Figures 5a, 5b and 5c. *See*, right-hand columns in Figures 5a, 5b and 5c. Accordingly, Applicants respectfully maintain that the data described on pages 37-38 and in Figures 5a-c clearly show that differentiating a neural stem cell in a growth medium supplemented with HGF and FGF-2 results in a differentiated population of cells that comprises more neurons (*e.g.*, more than 50%) than glia cells (*e.g.*, less than 40%).

With respect to claims 19-21, Applicants do not agree with the Examiner's position. The subject matter of a claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. M.P.E.P. § 2163.02. Furthermore, support can be provided through implicit or inherent disclosure. M.P.E.P. § 2163. However, in the interest of furthering prosecution, Applicants have canceled claims 19-23.

***Rejection under 35 U.S.C. § 102(e)***

The Examiner has rejected claims 4-6 and 8 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,589,728 ("Csete"). This rejection is respectfully traversed for the reasons discussed below, and in previous responses.

As the Examiner appreciates, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. § 2131, *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure.' M.P.E.P. § 2121.01, *citing In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The Federal Circuit has repeatedly affirmed the requirement that a reference must be enabling in order to defeat novelty. *See, e.g., Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); and *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374, 58 USPQ2d 1508 (Fed. Cir. 2001) ("To anticipate, the

reference must ... enable one of skill in the art to make and use the claimed invention.") The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. M.P.E.P. § 2121.01, *citing Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

Here, the claimed methods require culturing or differentiating a neural stem cell in cell culture to a growth medium supplemented with a combination of growth factors *consisting of* hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2). Applicants have amended claims 4-6 to set forth language that excludes supplementing the growth medium with growth factors other than HGF and FGF-2.

Csete does not expressly disclose or suggest culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF) and FGF-2. Csete also does not implicitly or inherently disclose or suggest culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2.

The Examiner appears to be basing this rejection on the passage located at column 7, lines 42-62 in Csete. This passage refers generally to undefined stem cells/progenitor cells, but does not call out neural stem cells in particular. This passage discloses that the [culture] medium can be supplemented with a variety of growth factors, cytokines, serum, etc and proceeds to list at least 11 different growth factors (basic fibroblast growth factor (bFGF)(1), vascular endothelial growth factor (VEGF)(2), epidermal growth factor (EGF) (3), transforming growth factors (TGFα and TGFβ) (4 and 5), platelet derived growth factors (PDGF's) (6+), hepatocyte growth factor (HGF) (7), insulin-like growth factor (IGF)(8), insulin(9), erythropoietin (EPO)(10), and colony stimulating factor (CSF)(11)), at least 4 different hormones, and at least 3 different cytokines. There is absolutely nothing in this passage in column 7 of Csete to disclose or suggest *combining* any medium supplement with another media supplement, much less a growth factor with another growth factor, or with a hormone or a cytokine. But Applicant's invention is a selection invention that requires culturing, proliferating

or differentiating a neural stem cell in particular by supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2 in particular. Csete certainly does not expressly disclose or implicitly suggest in column 7, or elsewhere, particularly combining HGF and FGF-2 and using growth medium supplemented with HGF and FGF-2 to culture, proliferate or differentiate neural stem cells in particular.

The only place where Csete does particularly disclose isolating, culturing and differentiating neural stem cells is in the section located at column 15, line 40 through column 16, line 24. Here, Csete discloses that nerve growth factor (NGF) promotes the growth of neural cells. Csete at column 15, lines 49-50. Csete also refers to U.S. Patent No. 5,750,376 ("Hazel and Muller"), which discloses proliferating neuroepithelial cells in medium supplemented with bFGF. Hazel and Muller disclose that in order to induce differentiation to neurons and glia, the medium containing bFGF is removed and replaced with medium lacking bFGF. Csete at column 15, lines 63-65. Nowhere in Csete is it disclosed or suggested to supplement a medium with ***hepatocyte*** growth factor to culture, proliferate or differentiate ***neural*** stem cells preferentially into ***neurons***.

The Examiner maintains the present anticipation rejection despite the particular disclosure in column 15 of Csete, because Csete generally discloses that for any stem cell/progenitor, the medium for proliferation and differentiation can be the same or different. *See*, Csete at column 7, lines 42-45 and the present Office Action at page 6. However, Csete have already provided information regarding the particular proliferation and differentiation medium for neural stem cells. According to Csete, neuroepithelial stem cells are initially cultured or proliferated in medium containing bFGF; to induce differentiation to neurons and glia the medium containing bFGF is removed and replaced with medium lacking bFGF. Csete at column 15, lines 54-65. According to the disclosures of Csete particular to neural stem cells, the proliferation and differentiation medium are different, and neither of them contain HGF. The differentiation medium for neural stem cells does not contain bFGF. Csete has provided specific information to the skilled person in column 15 for selecting from their long list of potential medium supplements in column 7 for isolating, culturing, proliferating and differentiating neural

stem cells in particular, and they do not teach or suggest the claimed methods, *i.e.*, combining HGF with FGF-2.

The Examiner refers to *Beckman Instruments v. LKB Produkter AB*, cited in M.P.E.P. § 2121.01 (II) for the proposition that even if a reference discloses an inoperative device, it is prior art for all that it teaches. *See*, page 6 of the present Office Action and page 2100-55 of the M.P.E.P. However, this quote is used in the context of a rejection under 35 U.S.C. § 103(a), and the present rejection is made under 35 U.S.C. § 102(e). The standard for properly citing a reference under 35 U.S.C. § 102 as set forth in M.P.E.P. § 2121.01 is recited above. To reiterate, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.

Applicants respectfully maintain the position that the passage at column 7, lines 42-62 of Csete is not enabling to those of skill regarding how to proliferate, culture or differentiate any kind of stem cell, much less neural stem cells in particular. The passage at column 7, lines 42-62 of Csete discloses a list of at least 18 potential medium supplements (11 growth factors, 4 hormones and 3 cytokines—glucocorticoids, interferons and interleukins are large, undefined genera in themselves) and does not teach or suggest which supplements to choose for which particular stem cell types (*e.g.*, skeletal muscle, neural, skin, embryonic, etc), *or whether the listed variety of medium supplements can be combined or how they would be combined* (*e.g.*, 2, 3, 4 or more supplements; multiple growth factors, a growth factor and a cytokine, etc.). If one of skill were to select two of the 18 listed medium supplements and combine them, there would be 17+16+15+14+13+12+11+10+9+8+7+6+5+4+3+2+1=153 different combinations. This number is much larger when considering the full breadth of interferons, interleukins and glucocorticoids and the numerous different stem cell types that could be selected. The courts have found undue experimentation for fewer permutations.

Csete provides ***no guidance*** in column 7 as to which medium supplements to select or for which kind of stem cell. Csete does provide guidance particular to culturing, proliferating and differentiating neural stem cells in column 15, and this disclosure does not teach or suggest the claimed methods. Nowhere does Csete teach or suggest culturing,

proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF) and FGF-2. The Examiner is respectfully reminded that the particular teachings of Csete with respect to neural stem cells in column 15 can not be ignored in favor of the general, non-enabled disclosure in column 7.

In view of the foregoing, it is clear that Csete does not disclose or suggest the present methods, either expressly, implicitly or inherently. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***Rejection under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 4-7 under 35 U.S.C. § 103(a) as allegedly rendered obvious by Csete in view of U.S. Patent No. 6,589,728 ("Luskin").

The Examiner has the burden of presenting a *prima facie* case of obviousness. For an invention to be obvious under 35 U.S.C. § 103(a) requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)).

Here, Applicant's respectfully maintain that the Examiner's articulated reasons for alleged obviousness do not have sufficient rational underpinnings to support a legal conclusion of obviousness. No *prima facie* case of obviousness has been established. Regardless, Applicants have rebutted any *prima facie* obviousness rejection by a showing of surprising and unexpected results.

No *Prima Facie* Case of Obviousness Has Been Established

Foremost, Applicants respectfully maintain their position that no *prima facie* case of obviousness has been established. For the reasons discussed above, Csete does not teach or suggest any method of culturing, proliferating or differentiating a neural stem cell by

supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2. Luskin does not supply the elements missing from Csete, and the combined disclosures of Csete and Luskin do not teach or suggest any method of culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2.

The Examiner states that Applicants' arguments presented in the previous response regarding the general disclosure of Csete at column 7 in contrast with the particular disclosure of Csete with respect to neural stem cells at column 15 are not persuasive. The Examiner reasons that although Csete expressly and particularly teaches in column 15 that neural stem cells are proliferated in medium containing bFGF or NGF, and differentiated in medium without bFGF, the general disclosure at column 7, lines 42-45, applying to any stem cell type, overrides this. The Examiner states, in direct contradiction to the express and particular disclosure of Csete at column 15, lines 63-65, that the same proliferating medium containing FGF-2 may thus be used for differentiation. *See*, page 9 of the present Office Action. Applicants respectfully disagree with the Examiner's reasoning. The specific teachings of Csete at column 15 teach the skilled person which medium supplements from the long list in column 7 to select for neural stem cells, and that the proliferation and differentiation media for neural stem cells are different: whereas the proliferation medium can contain NGF or bFGF, the differentiation medium does not contain bFGF. Neither contain HGF.

The facts of the present case are analogous to those presented in *In re Brian W. Baird*, 16 F.3d 380; 29 USPQ2d 1550 (Fed. Cir. 1994). In *Baird*, the claims at issue were directed to a toner comprising a bisphenol A polyester containing an aliphatic dicarboxylic acid selected from the group consisting of succinic acid, glutaric acid and adipic acid. The Examiner alleged the claims were obvious over a patent that disclosed developer compositions comprising the polymeric esterification product of a dicarboxylic acid and a generic diphenol. The generic disclosure of the cited reference disclosed a broad range of different diphenols, including bisphenol A. The Federal Circuit noted that although the general disclosure of the cited reference encompassed the particular species (*i.e.*, bisphenol A) recited in the claim at issue, there were no teachings suggesting to the skilled person to particularly select the species recited

in the claim. Instead, where the reference taught particular species they taught away from bisphenol A and focused on more complex diphenols. The Federal Circuit held that a disclosure to a large genus does not render obvious a claim to a species, particularly when that disclosure indicates a preference leading away from the claimed species.

In this case, like the facts in *Baird*, the general disclosure of Csete at column 7 provides absolutely no suggestion to the skilled person as to which medium supplement(s) that will benefit culturing, proliferation or differentiation of any particular stem cell type. Where specific teachings are offered in column 15 of Csete, the methods for proliferating and differentiating neural stem cells teach away from the present methods. Analogous to the facts of *Baird*, the disclosures of Csete particular to neural stem cells do not disclose or suggest culturing, proliferating or differentiating neural stem cells in medium supplemented with HGF, and in fact specifically teach removing bFGF to promote differentiation to neurons and glia.

The Examiner refers to M.P.E.P. § 2123(II) and cases cited therein for the proposition that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *See*, page 9 of the present Office Action. In response, Applicants respectfully assert that this section is inapposite to the facts of the present case. The generalized listing of medium supplements in column 7 of Csete teaches nothing and can not reasonably be interpreted as alternative or nonpreferred embodiments. Csete does not suggest ***any*** correlation in column 7 between a particular stem cell type and a medium supplement or supplements useful for culturing, proliferation or differentiation of that stem cell type.

Rebuttal of *Prima Facie* Obviousness by Showing of Surprising Results

Without conceding the any *prima facie* case of obviousness has been established, Applicants respectfully maintain their position that any *prima facie* case of obviousness has been rebutted by a showing of synergistic (*i.e.*, more than additive) effects of HGF and FGF-2. Moreover, a *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471,

43 USPQ2d 1362, 1366 (Fed. Cir. 1997). For the reasons discussed above, Applicants have shown that the primary reference, Csete, teaches away from the present methods.

The Examiner states that the demonstration of synergistic effects on HGF and FGF-2 is not persuasive because it is not clear why an increase in proliferative capacity of the cells in the presence of growth factors additional to HGF alone would be considered unexpected. *See*, page 10 of the present Office Action. In response, Applicants respectfully point out that the Examiner has apparently misunderstood Applicant's statements. Whereas the Examiner states that it is not unexpected for the addition of a second growth factor to have an additional effect or increase in proliferation capacity, Applicants have provided actual data in Table 1 on page 35 showing that the increased effects on proliferation and growth neural stem cells of a combination of HGF and FGF-2 are ***synergistic*** (*i.e.*, ***more than additive*** than either HGF or FGF-2 individually). That is, the unexpected result is not that the proliferation and growth of the neural stem cells merely increased *per se*, but that the increase was ***synergistic*** (*i.e.*, ***more than additive***). In stark contrast, the combination of EGF and FGF-2 had increased effects on proliferation and growth neural stem cells that were clearly NOT synergistic and ***less than additive*** than either EGF or FGF-2 individually. *See*, Table 1 on page 35 of the Specification. Applicants maintain that the skilled person would have no *a priori* reason to predict that the combination of HGF and FGF-2 would have synergistic effects on the proliferation and growth of neural stem cells and that the combination of EGF and FGF-2 would have less than additive effects.

The Standard for Inherency Has Not Been Met

Finally, the Examiner appears to be basing the present obviousness rejection (and the present anticipation rejection) on the inherent disclosure of Csete, presumably based on the disclosure in column 7, lines 42-62. *See*, page 11 of the present Office Action. Applicants agree that Csete does not expressly disclose or suggest any method of culturing, proliferating or differentiating a neural stem cell by supplementing a growth medium with a combination of growth factors *consisting of* HGF and FGF-2. Applicants also respectfully maintain that the Examiner has not met the standard for inherency.

As the Examiner appreciates, in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *See*, M.P.E.P. § 2112 (IV), *citing Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *See*, M.P.E.P. § 2112 (IV), *citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), and *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Moreover, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Id.*, *citing In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Moreover, any rejection which is predicated upon "inherent obviousness" is simply in error. As quoted with acceptance in *In re Rijckaert*, *supra*, at page 1957:

> ..."That which is inherent is not necessarily known.
> Obviousness cannot be predicated on what is unknown."
> (citations omitted)

Such is the case here. In the long list of medium supplements disclosed in column 7, lines 42-62 of Csete, including growth factors, cytokines and hormones, Csete does not teach or suggest combining any supplements, much less particularly two or more growth factors, much less the growth factors of HGF and FGF-2 in particular, ***and*** using the combination of HGF and FGF-2 to culture, proliferate and differentiate neural stem cells. The affirmative selection of HGF and FGF-2 as supplements to growth medium for the particular purpose of culturing, proliferating and differentiating neural stem cells does not necessarily exist anywhere in Csete or Luskin.

Furthermore, an invitation to investigate is not an inherent disclosure where a prior art reference discloses no more than a broad genus of potential applications of its

discoveries. *Id.*, *citing Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.).

Here, the long list of medium supplements listed in column 7 of Csete do not in any way call out the selection of the combination of HGF and FGF-2 (or any other combination of medium supplements) for the culturing, proliferation or differentiation of neural stem cells. To the extent that the disclosure in column 7 is even an invitation to investigate, Csete provides specific guidance in column 15 to the skilled person for the growth, proliferation and differentiation of neural stem cells: HGF is not included in the medium, and FGF-2 is removed in order to induce differentiation to neurons and glia cells. Because the selection of a combination of HGF and FGF-2 for use in the culturing, proliferation and differentiation of neural stem cells does not necessarily flow from the disclosure of Csete, this reference does not inherently render obvious or anticipate the present methods.

Summary

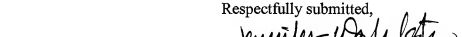
For the foregoing reasons, the combined disclosures of Csete and Luskin do not render the present invention obvious. In any instance, Applicants surprising results properly rebut any *prima facie* case of obviousness.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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